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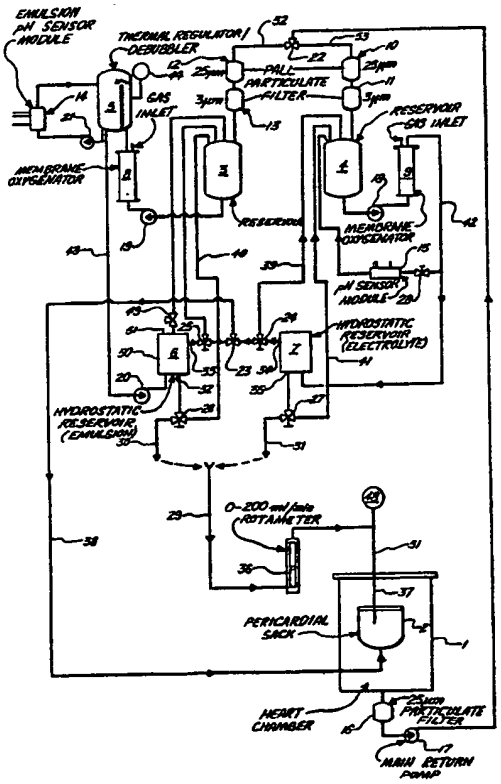
(57) Abstract

The system enables an organ to be maintained extracorporally until it can be used as a donor organ in an organ transplant. The system uses a fluorocarbon primary perfusion emulsion (3) to feed nutrients to an organ (1) and to remove waste products from the organ. The solution introduced into the organ is oxygenated (8) and receives additional nutrient material (6) before it enters the organ. The system further maintains the appropriate temperature, pressure, oxygen concentration and pH of the nutrient fluid. The waste fluid (17) is filtered prior to being recycled to again provide oxygen and nutrients to the organ.



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TOTAL ORGAN PERFUSION SYSTEM

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to systems, including apparatus, fluid chemistries and procedures, for maintaining living biological organs or tissues. The invention relates particularly to a total organ perfusion system that allows a donor organ to be maintained extra-corporeally for an extended time period.

Transplant surgery and anti-rejection pharmacology have been improved such that transplant operations are now limited only by donor availability. There is consequently a need for a method and apparatus for maintaining a donor organ extra-corporeally for a given, extended time period, allowing that organ to be transported and maintained in a healthy condition until a recipient is prepared to receive the organ.

The Prior Art

Previous attempts at designing apparatus for preserving human organs extra-corporeally have been made. See, for example, U.S. Patent No. 3,753,865 to Belzer et al. Such systems pump human plasma through the donor organ at low temperatures. These low temperatures are important in these systems to keep the organ's biological activity at a minimum.

Attempts to design perfusion systems in the past have typically involved design criteria adapted to only one type of organ, i.e., kidneys, liver, heart, lungs, etc. An example of such a perfusion system is U.S. Pat. 4,186,565 to Toledo-Bereyra. As disclosed in U.S. Pat. 4,186,565, several methods of kidney perfusion have been used. Folkert O. Belzer, B. Sterry Ashby and J. Englebert Dunphy in Ann. Surg., 172:394, 1970, describe a system for

perfusion of kidneys by hypothermic pulsatile perfusion utilizing a pulsatile pump, a membrane oxygenator, a heat exchanger and a refrigeration unit. The perfusate was supplied by the pump through the heat exchanger and the oxygenator to the organ.

In another system described by A.W. Moberg, E.A. Santiago, R.V. Mason, M.J. Mozes, R.A. Campos and J.S. Najarian, in The Lancet, Dec. 25, 1971, a smaller self-contained system was provided utilizing an organ cassette which included an organ chamber, circulating fluid, membrane oxygenator and heat exchanger.

In a third type of system described by G. Claes, I. Blohme and L.E. Gelin in a paper to be published in proceedings from EDTA meeting in Berlin, July, 1971, a similar system was provided which included non-pulsatile perfusion, i.e., a pump that did not pulsate.

Other patents of interest include Michielsen, U.S. Pat. No. 3,660,241, disclosing an organ chamber, and more particularly, an organ chamber that permits cannulation of an organ. DeRoissart, U.S. Pat. No. 3,772,153, discloses a refrigerated, pressurized environment for the perfusion of a living organ. Bier, U.S. Pat. No. 3,843,455, discloses a hypothermic perfusion system requiring heat exchange means.

Characteristics common to most prior art perfusion systems are their attention to pulsatile pressure and temperature control. See for example, Thorn, et al., U.S. Pat. No. 3,892,628, which discloses an organ preservation chamber where the improvement is described as a pump which develops a pulsatile pressure. Likewise, Doerig, U.S. Pat. 3,935,065, discloses a perfusion system in which the perfusate is cooled by a combination of dry ice and carbon

dioxide. Finally, Clark, et al., U.S. Pat. No. 3,995,444 discloses a perfusion system in which the improvement is described as a heat exchanger.

An article of general interest in characterizing organ preservation technology is "Organ Preservation: Current and Future Perspectives," Luis H. Toledo-Pereyra, Medical Instrumentation, Vol. 20, No. 2, Mar-Apr. 1986. The article identifies two methodologies for maintaining an organ in the living state ex vivo:

> Either the tissue metabolism may be reduced enough so that oxygen and energy carriers are unnecessary or one may attempt to meet as many of the requirements of normal metabolism as possible in the preservation setting.

The total organ perfusion system of the present invention instead uses an oxygen enriched emulsion as the oxygen-nutrient transport system to the organ interior. This emulsion allows the organ to be maintained at higher temperatures, compared to previous systems, under the control of a series of sensing devices which enable the control of the chemical composition of the fluid. Typically, the emulsion includes either a liquid fluorocarbon or porphyrin as active ingredients with micelles of less than 1 micron.

The total organ perfusion system of the present invention also permits the donor organ to be maintained over a broad range of temperatures as compared to previous systems. Organs perfused with the apparatus, chemistries and methods of this invention may be changed between normothermic and hypothermic conditions without tissue degradation (ischemia). The fluids used in this invention are high oxygen transference fluids. In many instances, these fluid compositions contain perfluorochemicals. Using the apparatus, chemistries and methods of this

invention, it is possible to place a donor organ or tissue sample into virtually a state of suspended hibernation similar to the state that the organs of hibernating animals reach.

Through the manipulation of biological trigger mechanisms thought to be tied to ionic potentials within the organ cellular chemistry, levels of ATP (adenosine triphosphate) control the biological function of the organ or tissue.

SUMMARY OF THE INVENTION

A total organ perfusion system is provided. The system includes an organ chamber for supporting an organ or other integrated tissue accumulation that has utility in the performance of bodily functions. This organ chamber is supplied with an emulsion fluid or physiological electrolyte that is transported through a perfusion system. Preferably the perfusion system both feeds the fluid into the organ interior and bathes the organ exterior. A filtering system filters particulate waste, including bacteria and cellular debris, from the fluid that bathes and supplies nutrients to the organ. This fluid is pumped through a transportation system, allowing particulate and toxic species to be removed from the fluid and allowing the fluid to be re-oxygenated prior to returning to the organ chamber.

It should be understood that for purposes of simplicity, a substantial portion of the description and elements of this application are described as relating specifically to the extra-corporeal maintenance of a heart or heart tissue. This is not intended as a limitation on the application of the method, chemistries or apparatus of this invention. The system is equally adaptable to the

extra corporeal maintenance of any other body organs or whole tissue samples such as lungs, liver, kidneys, the heart, and other tissues which are capable of donation by an individual.

The functional capability of the organ perfusion system of this invention requires the maintenance of a delicate balance between the chemistries of the perfusion fluids and the perfused organ. The biological key to the successful maintenance of organs or tissue is the ability to maintain the correct electrolyte balance on either side of the cell membrane with a minimum of ATP usage by the organ or tissue. The ultimate goal is to have cells, specifically heart tissue cells, optimized in their ability to produce contractions. For example, successful perfusion requires that sodium and calcium ions be kept outside the cell membrane and potassium within. This is a key element in maintaining low edema and low ATP usage by the sodium/potassium pump. It is essential that ion concentrations and thus electrolyte concentrations of sodium, potassium and calcium be maintained at appropriate levels.

In addition to permitting organ transplantation and maintenance, the practice of the perfusion system of this invention enables the user to have extended time periods for the study of the physiology of tissue or organs. This will permit investigation of the intent of the organ and its performance. It will be possible to now measure the "performance" of organs under normothermic conditions. Practice of this invention permits study of organs and organ reactions in the "living state," i.e., the state of full metabolic activity.

The method, chemistry and apparatus of this invention permit the repair of a donor organ while at normothermic

temperatures. This will likely be a critical area for organ transplantation. This would be especially important if the particular organ being transplanted was one that is subject to tissue rejection. Use of this invention will permit a diseased or otherwise malfunctioning organ to be surgically removed from a patient and cleansed, cured or otherwise modified extracorporally, and then surgically reimplanted in the same patient. The result of such a procedure would be elimination of rejection as an organ transplant problem.

The methods, chemistries and apparatus of this invention will further permit experimentation on drugs or therapeutic agents to identify their specific effects on isolated organs or tissues. Finally, and potentially most importantly, the methods, chemistries and apparatus of this invention will permit the low temperature oxygen starvation of organ or tissue to selectively kill diseased tissue which typically have an oxygen consumption rate significantly greater than that of normal tissue. This may be especially effective in the treatment of cancer.

In a preferred form of this invention for use with a heart, two separate infusion media are employed. Each is circulated, filtered and oxygenated prior to infusion into the interior and around the exterior of the perfused organ within the organ support chamber. One perfusion system utilizes a physiological electrolyte perfusate with levels of potassium allowing reduced sodium/potassium pump activity. Another perfusion system utilizes a fluorocarbon or iron/magnesium porphyrin pseudoplasma emulsion as the oxygen nutrient transport system. The emulsions must be of a particle size below 0.2 microns to allow passage through the filter for bacterial removal. A third and optional perfusion system is referred to as a shunted perfusion system which allows short-term perfusion

of organs with heparinized whole blood for injury repair and preparation/conditioning of the organ prior to processing, i.e., medical research, transplantaion or the like.

The perfusion system is of critical importance to the practice of this invention. The physiological electrolyte solution contains electrolytes, water soluble waste products, nutrients and proteinaceous species and is substantially filtered and dialyzed in the perfusion system. A micro filter and hollow fiber dialyzer utilizing carbon and synthetic sorbants is used to remove toxic species prior to UV sterilization of the fluid.

Another composition used as a perfusion medium is a fluorocarbon/lipid hydrophobic emulsion. This fluid is passed through a medium polarity grafted sorbant, thin film ultraviolet sterilizer, fluorocarbon to lipid analyzer, fluorocarbon/lipid addition and oxygenation cell and micro filtration cell prior to injection into the emulsifier.

Importantly, the perfusion fluids of this invention, and specifically the primary perfusion chemical system, contains no cellular components such as red blood cells, white blood cells, platelets, or the like, or immuno-proteins, for example, Ig series or compliment. Direct peroxide addition, ultraviolet sterilization, and high pressure filtration, not possible with cellular constituents present, allows the maintenance of sterility without the presence of cellular or humoral immunological species.

The deemulsification system found in this perfusion system allows the hydrophilic and hydrophobic toxins to be

removed separately utilizing the most efficient dialysis/sorbant technology.

Oxygenation of the perfusates can be accomplished directly by exposure to oxygen gas or by addition of peroxide to the fluid followed by ultraviolet exposure of the fluid in the oxygenation chamber. In the emulsion fluid, fluorocarbon droplets, stabilized by lipo proteins, can be viewed as artificial red blood cells. As the fluorocarbon droplets are "fouled" by hydrophobic toxins and lipids, the fluid is replaced. Glucose, dextran, lipids, phospho-lipids and albumin are added as needed for nutrition, viscosity and osmotic pressure maintenance.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic drawing of the specific components used in a preferred embodiment of the total organ perfusion system of this invention.

FIG. 2 is a schematic drawing of an embodiment of the refrigeration system that may be used in conjunction with the total organ perfusion system.

FIG. 3 is a schematic drawing of an embodiment of the oxygenation delivery system that may be used in conjunction with the total organ perfusion system.

FIG. 4 is a schematic drawing of an embodiment of the control system that may be used in conjunction with the total organ perfusion system.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

As described hereinbefore, the apparatus, chemistries and methods of this invention are described primarily as they relate to the extracorporeal maintenance of a heart. This is, however, not to be considered a limitation on the application of the technology of this invention, but merely exemplary thereof. For purposes of this invention, numerical reference is made to certain components of the apparatus of this invention. The numbers are intended to be references to the figures found in the drawings. Like numbers in the text and figures are intended to reference like components of this invention.

FIG. 1, FIG. 2, FIG. 3 and FIG. 4 are schematic diagrams of a preferred embodiment of the present invention. In this embodiment, the total organ perfusion system of the present invention is used to maintain a human heart extracorporeally.

The system includes a heart chamber 1, which contains a polyurethane synthetic pericardial sac 2 in which the heart (not shown) is positioned. The system has been designed such that the heart can be perfused in the heart chamber 1 from external fluid sources fed into, and removed from, the chamber by 12 volt D.C. gear pumps.

The described system incorporates two independent fluid sources, each of which includes two reservoirs. As a result, this apparatus is capable of maintaining and perfusing the heart with either a physiological perfusate solution (secondary electrolyte solutions) or the aforementioned fluorocarbon pseudoplasma perfusate (primary emulsion). A perfusate solution can either be fed into the heart chamber 1, to perfuse the organ, or recirculated between the two described reservoirs. During

both the perfusion or recirculation modes, each of the perfusate solutions is maintained at preset pH, temperature, and oxygen concentration levels. Perfusate solution pumped into the heart chamber perfuses the heart by entering the organ via a catheter positioned in the aorta through a branch artery. This configuration permits retro-perfusion of the coronary arteries which exits fluid into the right ventricle. Fluid in the right ventricle egresses through the surgically exposed main vessel orifices and into the pericardial sac 2.

Recirculation of a physiological electrolyte perfusate is performed in a fluid circuit comprising reservoir 4, membrane oxygenator 9, pH sensor module 15, and hydrostatic reservoir 7. Recirculation is affected by pump 18 which withdraws fluid from the bottom of reservoir 4, pumps it through the membrane oxygenator 9, where the perfusate is oxygenated, and is finally pumped into the hydrostatic reservoir 7. Recirculation valves 24 and 27 are positioned such that fluid exiting this reservoir, through either the bottom port 35 or overflow port 34, returns back to reservoir 4 via lines 39 and 41. A small quantity of fluid diverted from line 42 is pumped through pH sensor module 15 by regulating manual valve 28.

Recirculation of fluorocarbon emulsion, which can occur simultaneously with electrolyte perfusate, involves the transport of fluid from reservoir 3 to the thermal regulator/debubbler 5, via membrane oxygenator 8, by action of pump 19. Level detector 44 regulates the amount of fluid that pump 19 charges into the debubbler by turning the pump on and off. Fluid from the debubbler is infused into hydrostatic reservoir 6 by pump 20. Recirculation valves 25 and 26 are positioned such that fluid exiting the hydrostatic reservoir 6, through ports 32 and 33, is returned to reservoir 3. In addition to

this fluid routing, a small quantity of the emulsion is circulated through pH sensor module 14 by pump 21.

Perfusion of the explanted heart in the heart chamber 1 by one of the perfusates is performed by re-directing recirculating fluid, exiting a hydrostatic reservoir, into the main perfusion inlet line 29 and the pericardial sac inlet line 38. For instance, to initiate perfusion with recirculating fluorocarbon emulsion, manual valves 25 and 26, in addition to solenoid valves 22 and 23, must be switched such that fluid egressing from hydrostatic reservoir 6, through ports 33 and 32, feeds into lines 38 and 30. Lines 30 and 29 must be manually connected in order to permit the transport of emulsion into the heart via the flowmeter 36 and the arterial catheter 37. In this configuration, perfusate also enters the heart chamber 1 through the bottom of the pericardial sac 2 by way of line 38. This fluid bathes the exterior of the organ and mixes with the solution exiting from the right side of the heart. This fluid then overflows from the pericardial sac 2, collecting at the bottom of the heart chamber 1, before being removed by pump 17. Pump 17 draws fluid from the heart chamber 1 through filter 16 and pumps it back to reservoir 3 via filters 12 and 13. This completes a closed loop perfusion circuit.

Perfusion of the heart with electrolyte solution requires that manual valves 25 and 26 and solenoid valve 23 be switched such that the emulsion solution reverts back to the recirculation mode. Manual valves 24 and 27 are then switched in order to direct fluid from the electrolyte hydrostatic reservoir 7 into lines 38 and 31. Finally, line 31 is substituted for line 30 to permit electrolyte solution perfusion of the heart. Solenoid valve 22 is switched to direct perfusate, exiting the heart chamber, into reservoir 4 via filters 10 and 11.

FIG. 2 describes the cooling/heating circuits incorporated in the total organ perfusion chamber and interfaced to external refrigeration units. There are two circuits in this apparatus, one for cooling the electrolyte perfusion below 10°C and the other to maintain the emulsion perfusate at 37°C. The electrolyte perfusate solution is cooled from refrigerant coils immersed in reservoir 4 and hydrostatic reservoir 7. Fluid passing through this circuit can also be directed into hydrostatic reservoir 6, containing the fluorocarbon emulsion, should the temperature exceed 37°C, by action of solenoid valve 45. Solenoid valve 45 is automatically controlled by a sensing circuit which employs an RTD thermal element positioned in reservoir 6. Sustaining the emulsion at 37°C is maintained by heating coils immersed in reservoir 3 and thermal regulator 5.

FIG. 3 describes the gasification system of the total organ perfusion system. Oxygenation and stabilization of the fluid pH is provided by 100% oxygen and 95% oxygen/5% carbon dioxide transferred to the electrolyte and emulsion perfusates in the membrane oxygenators 9 and 8, respectively. The introducton of the oxygen/carbon dioxide gas mixtures is capable of reducing high solution pH when fed into the membrane oxygenators. Separate pH control circuits for each perfusate solution are utilized to control solenoid valves 46 and 47, which direct either oxygen or the oxygen/carbon dioxide gas mixture into the membrane oxygenators, depending on the pH of the solution. For instance, if the electrolyte perfusate pH were to rise above 7.7, solenoid valve 46 would be activated, causing the introductin of carbon dioxide/oxygen into the membrane oxygenator.

FIG. 4 describes the control systems incorporated in the described TOPS Mother Unit design. Control systems

are employed to control: (1) level of fluid in the debubbler/oxygenator module 5, (2) pH of the fluorocarbon emulsion perfusate, (3) pH of the electrolyte perfusate, (4) temperature of fluorocarbon emulsion perfusate, and (5) pressure of perfusate introduced to the coronary vessels of the perfused heart.

The fluid level of perfusate in the debubbler/thermal regulator unit 5 is controlled by level detector 44 which shuts off pump 19 when a threshold level is achieved. The level detector is based on the interruption of an IR beam, between an IR-emitting LED and an IR-detecting phototransistor, by a float which ascends/descends with varying fluid levels.

The pH of emulsion perfusate is detected by the emulsion pH sensor module 14, from which a signal is sent to the pH sensor (emulsion) (not shown). This module activates/deactivates solenoid valve 47 when the high and low setpoints on this controller are reached. These set-points are manually set by the operator. A similar control system is employed to activate/deactivate valve 46 for pH detected in the electrolyte perfusate by the pH sensor in pH sensor module 15.

A temperture control system is incorporated into the heating/cooling system for the emulsion (described in FIG. 3). An RTD temperature element 50, positioned in the hydrostatic reservoir 6, sends a signal to a temperature controller (not shown) which activates solenoid valve 45 when the emulsion temperature exceeds 37°C. This causes cooling fluid to circulate in the coil in 6.

To prevent excessive pressure generated by a contracting heart from increasing above physiologically acceptable levels, a pressure release control system has

been incorporated into the emulsion fluid delivery system. Pressure signals detected by the transducer 48 are sensed by a pressure controller (not shown). Should the pressure of the perfusate in the perfusion line 51 exceed a pre-established level, the pressure controller activates solenoid valve 49, which releases the back pressure in the hydrostatic reservoir 6, which rapidly decreases the pressure in the hydrostatic reservoir 6, and in turn, inside the heart.

Sensors may be placed in several locations in the system, allowing the instantaneous measurement of temperature, pH, and pO_2 of the perfusion medium. Such instantaneous measurement of these parameters may be important, because the proper maintenance of these parameters within specific ranges could be critical to the long-term survival of the heart tissue.

Included in this embodiment of the total organ perfusion system preferably is a conventional heart pacing mechanism used to induce and maintain a continuous steady heartbeat during normothermic testing to ensure that the heart has been maintained in a viable, transplantable condition. Typically, however, the heart beats without pacer stimulation during normothermic testing.

Most of the components of the total organ perfusion system are available commercially. The heart chamber preferably is a 4-1/2 gallon Nalgene polycarbonate tank (Cole-Parmer Instrument Company, Cat. No. R-6761-07). Reservoirs 3 and 4 preferably are 1/2 gallon Nalgene polycarbonate tanks (Cole-Parmer Instrument Company, Cat. No. TV-6761-20). Hydrostatic reservoirs 6 and 7 are preferably 1/4 gallon Nalgene polycarbonate tanks (Cole-Parmer Instrument Company, Cat. No. R-6761-15).

The cardiac catheters that may be used are conventional (USCI Extracorporeal Circulation Cannulae, Vennous Catheter, Cat. No. 007208). The pumps 18-20 used in the system may include miniature 12 VDC gear pumps (Cole-Parmer Instrument Company. Part #R-7009-50). Pump 17 is preferably an Ismatec gear pump (Cole-Parmer Instrument Company Part #J-7617-75).

The solenoid valves preferably are 3-way plastic body solenoids (Automatic Switch Company, Model #8360A74). The level detectors are preferably a lab assembled fiber optics interfaced photodiode/photodetector control system that includes a IR photodiode/photodetector set (Radio Shack, Cat. No. 276-225). This system may be assembled with a relay circuit board.

Temperature sensor 50 is preferably a platinum resistance thermometer (Omega Engineering, ITT-100, Model #G12-30). The controller used to transform signals from the temperature sensors to signals to the solenoid valves is also conventional (Omega Engineering RTD Digital Controller, Model #4204-PF2-T).

The pH sensors are conventional (Cole-Parmer Instrument Company, Digi-sense pH Meter, Cat. No. BA-5985-80). A pO_2 sensor (not shown) preferably includes an oxygen probe (Cole-Parmer Instrument Company, Cat. No. R-5948-52) and an oxygen meter (Cole-Parmer Instrument Company, Cat. No. R-5948-50).

Pressure gauges 52 and 53 are preferably 0-5 psi pressure gauges (Marsh Instrument Company). Pressure transducers 48 and 51 are also easily obtained (Omega Engineering, Cat. No. PX242-005G, PST-8, and DP2000-P4 and Cole-Parmer Instrument Company, Cat. No. 12-6373-45).

Particulate filters 10-13 are commercially available for use in the present system (Millipak 50, Millipore Products; Ultipor Filter Assembly, VWR Scientific).

The assorted valves and tubing used in this system are conventionally available; silicon and polyethylene tubing is preferred. The membrane oxygenator is conventional (Scimed Life Systems, Model No. 0400-2A). The cardiac pacemaker, thermal regulator debubbler and sensor module may be fabricated by those skilled in the art for use with a particularly designed system.

The Perfusion Systems

Although the apparatus of this invention and hypothermic conditions created by the apparatus are important elements of the preservation goals of this invention, the chemistries of the fluids circulating through the organs or tissue are likewise essential. As mentioned previously, the control of electrolyte concentrations at membrane wall interfaces is an essential function of the solutions flowing through the apparatus and contained organ. The ions that need to be controlled include, but are not limited to, chloride, sodium, potassium, calcium, magnesium, and phosphates. At the various membrane walls present in the organs and tissue of this invention, there is a potential difference which is the direct result of ATP consumption. By maintaining the potential difference within defined ranges, the biological activity of the component cellular structures of the organ can be maintained within acceptable limits.

In one preferred embodiment of this invention, there is used a perfusion system which injects fluids throughout the interior of the organ via cannulation devices and a perfusion system which circulates fluids on the outside of the organ. In many instances, maintaining the separation

between an interior and exterior fluid is difficult due to leakage in the hardware associated with the system as well as leakage from the interior to the exterior of the organ itself, i.e., via surgical sutures and the like. Therefore, in a second preferred embodiment of the invention, the same perfusion fluid is circulated both externally and internally to the organ.

The primary perfusion emulsion is intended to provide virtually the same body functions as whole blood. A commercially available primary perfusion emulsion material is manufactured by the Green Cross Corporation of Japan and is identified as FC-43 Emulsion. The FC-43 emulsion is a perfluorochemical artificial blood, which is advertised as having utility for experimental studies in physiology, biology, biochemistry, chemotherapy, toxicology and metabolism studies. Functionally, the primary perfusion fluid is required to transfer oxygen and other biological nutrients to organ tissue. Therefore, oxygen must be soluble in at least one of the components of the primary perfusion emulsion. One such family of material that has achieved commercial significance is generally identified as perfluorochemicals. Oxygen is highly soluble in liquid perfluorochemicals. Whereas normal saline or blood plasma dissolves about 3% oxygen (by volume) and whole blood about 20%, pure perfluorochemicals dissolve 40% or more.

Another parameter that is essential in the design of the primary perfusion emulsion is the size of particles present in such an emulsified solution. Particles larger than erythrocytes, which are about 7-10 microns in diameter, will not pass through small capillaries and thus increase the risk of embolism. It is therefore important that the primary perfusion emulsion have an average particle size which is appropriate for use in a capillary

system and which will maintain the oxygen transfer function of whole blood for an indefinite period of time.

In designing the primary perfusion emulsion, it is essential that the component materials include oxygen exchange and transport chemicals, i.e., perfluorochemicals, and at the same time, be suitable for transport in the capillary system of the organ or tissue being perfused. It is also essential that the primary perfusion emulsion not be toxic to the organ or tissue nor have any deleterious side effects.

The secondary perfusion fluid includes an extra cellular electrolyte solution, an intracellular electrolyte solution, an intermediate solution and a transfer solution. Depending on the particular organ or hardware configuration, one or more of the secondary perfusion solutions may be omitted.

Various secondary perfusion fluids are used to supplement the primary perfusion emulsion to achieve a specific effect. The secondary perfusion fluids described in this application are meant primarily for the preservation of a heart organ or heart tissue. Therefore it is important that contractions and expansions of the heart muscle be controlled.

The extracellular electrolyte solution is used to control the electrolyte concentrations at the cell membranes in the heart. A typical formula for the extracellular electrolyte solution is found in Table I herein below.

TABLE I
CHEMICAL COMPOSITION OF PERFUSATE

Component	Quantity	Units
NaCl	6.8	gm./liter
KCl	0.44	gm./liter
$CaCl_2$ $2H_2O$	0.441	gm./liter
EDTA	0.146	gm./liter
$MgSO_4$ $7H_2O$	0.295	gm./liter
Na H_2PO_4 H_2O	0.166	gm./liter
$NaHCO_3$	2.1	gm./liter
Dextrose	2.9	gm./liter

By increasing the sodium ion concentration through infusion of the extracellular electrolyte solution into the primary perfusion emulsion, the heart can be frozen in contraction.

The intracellular electrolyte solution functions in much the same way as the external solution, although it is important that the electrolyte materials internal to the system also maintain the electrolyte charge across the cell membrane within acceptable parameters. A typical composition for the intracellular electrolyte solution is found in Table II:

TABLE II
CHEMICAL COMPOSITION OF PERFUSATE

Component	Quantity	Units
$NaHCO_3$	1.26	gm/liters
K_2HPO_4 $3H_2O$	9.7	gm/liters
KH_2PO_4	2.05	gm/liters
$KHCO_3$	2.3	gm/liters
KCl	1.12	gm/liters
$MgSo_4$ $7H_2O$	7.4	gm/liters

Glucose	2.0	gm/liters
Mannitol	25.0	gm/liters

By increasing the potassium ion concentration, the hypothermic cell membrane potential can be maintained.

The intermediate secondary perfusion solution is described sometimes as a Krebs solution or a cardioplegic solution. The intermediate solution is an organ stopper in which the organ is stopped, but not frozen. The primary function of the intermediate solution is to increase the sodium ion concentration in relationship to the potassium ion concentration. Finally, the transfer solution is typically the same as the extracellular electrolyte solution with more calcium ion. The transfer solution is used during transfer of the organ or tissue.

In perfusing the isolated organ or tissue with both the primary perfusion emulsion and necessary supplementation from secondary perfusion solutions, the variables that must be maintained and monitored are pH, temperature, oxygen partial pressure and fluid pressure. Acceptable ranges for the heart organ for each of these variables are:

pH	-	6.8 to 8.0
Temperature	-	Normothermic 37°C ± 1°C Hypothermic 4 to 6°C
Oxygen Partial Pressure	-	Normothermic 600-750 min. Hg. Hypothermic 150-300 min. Hg.

Fluid Pressure - Normothermic 40-120 min. Hg.
Hypothermic < 20 min. Hg.

The Method

The method of this invention is very important, but is specific to each type of organ or tissue sample that is to be maintained or perfused. For purposes of this application, the method will be described in terms of the steps and procedures necessary to perfuse and maintain a heart. This basic procedure may be modified to permit maintenance or perfusion of other organs or tissues. The description of the method of this invention in conjunction with the maintenance/perfusion of a heart is not intended to be limiting on the scope of this invention, but merely exemplary of the procedures which are characteristic of use of the apparatus and chemistries of this invention.

Prior to explanting the heart, it is essential to first check the flow system and sensors in the overall perfusion system. The pumps, solenoid valves, level controllers and refrigeration units are checked for functional characteristics. The sensors and controllers are then checked to verify that temperatures, pH, pressure transducers and radiometer oxygen partial pressure and carbon dioxide partial pressures are accurately measured and calibrated. The perfusate systems are also checked for component concentrations.

The primary perfusion emulsion, such as the FC-43 solution disclosed earlier, is prepared immediately prior to use by mixing the two electrolyte solutions with the pre-mixed emulsion. The resulting emulsion is then charged into the reservoir of the perfusion system.

The temperature, pressure, flow rate and pH of the primary emulsion system are stabilized in the perfusion unit.

Next, the heart is surgically isolated pursuant to standard surgical protocol. A cardioplegia solution is administered. This solution consists of about 15-18 milliequivalents of potassium ion. The solution is administered to the heart via cannulation of the brachial artery. Subsequently, the main vessels are ligated and the organ is immersed in a saline/icewater bath to bring the temperature to 4°C. The temperature is decreased so the oxygen consumption is minimized.

Perfusion with the 4°C cardioplegia solution is initiated in conjunction with the primary perfusion emulsion. It is essential that there be no leakage in the aortic valve or aorta itself and therefore, the coronary perfusion pressure and the resultant coronary flow are checked. An approximate flow of 25-35 milliliters per minute per 10 millimeters of mercury pressure should be anticipated. For experimental purposes to measure the pressure via monitoring equipment, an empty balloon is inserted from the apex of the heart into the left ventricle. The balloon is then blown up by a syringe with water.

The flow rate of the primary emulsion fluid into the heart chamber is adjusted to 50 milliliters per minute. Following the initial perfusion, the arterial perfusion catheter is connected to the emulsion outflow tube. It is essential that bubble entrapment be avoided at the connection interface.

The emulsion to be delivered to the heart is stabilized at a temperature of 37°C ± 1/2°; a pH of 7.4 ±

.05 and a pressure of 100 millimeters of mercury; and a flow rate of 150-250 milliliters per minute. The flow rate is dependent upon the coronary resistance. Two pacemaker electrodes are sewn into the ventricular myocardium. Pacing with the custom pacer is set at 100 beats per minute, pulse width of 1.5 milliseconds and an amplitude of 5 volts.

The left ventricle balloon volume is increased until an end diastolic pressure (EDP) of 4 millimeters of mercury is attained. After 10 to 15 minutes of stabilization period, measurements from the left ventricle systolic pressure (SP) and EDP are recorded. Data for a complete pressure-volume curve (Starling's curve) are obtained by incrementing the balloon volume and recording the resultant ventricular SP and EDP for each increment. This pressure volume serves as a control curve for heart function.

After obtaining the pressure volume data, heart pacing is stopped, and the balloon is removed from the ventricle. The emulsion solution is drained from the perfusion system, the refrigeration units are set to 0°C, and the cardioplegia solution is charged into the unit containing the heart.

The cardioplegia solution is stabilized in the unit at 5°C ± 1°C, intraventricular pressure of 20 millimeters of mercury ± 5 millimeters of mercury, a pH of 7.6 ± 1, and a flow rate of 70 milliliters per minute ± 10 milliliters per minute.

With the perfusion system in place, the heart can be maintained indefinitely. It is likewise possible to raise the temperature of the heart if there is ATP depletion (which occurs more readily at low temperatures) and the

ATP can be replenished and the heart temperature then regulated to its low oxygen consumption level.

Example 1:

In this example, a dog heart is surgically isolated and maintained in the perfusion system. In the preparation system, the blood is removed from the dog and the normal blood volume is maintained by a rapid infusion of lactate or Ringer solution. The pericardium of the dog is opened, and standard surgical procedures are used to remove and isolate the heart.

The surgical procedure involves exposing the superior vena cava and inferior vena cava, suspending the pericardium with 2-0 silk suture, isolating the inferior vena cava and leave, as long as possible, a stalk of interior vena cava. Heavy silks are passed around the superior vena cava and around the azygous vein. The main pulmonary artery and ascending aorta are dissected free. The inominate and left carotid arteries are dissected. The animal is heparinized with 3 milliliters per kilo of heparin directly into the superior vena cava. The superior vena cava is tied off together with the azygous vein. The left common carotid is dissected and tied off and the proximal common carotid is clamped and a cannula is inserted into the ascending aorta.

After additional surgical procedures, the heart is allowed to beat several times so that the coronary return will pass through the lungs and will clear the blood from the lungs and the left heart. At this point, the aorta is clamped and the heart is surgically removed by transecting the pulmonary veins, the aorta distal to a clamp and large vessels. The heart is explanted at the same time that the cardioplegia solution is administered and the heart is then submerged in iced saline solution. The heart is then

inserted into the heart chamber and the cannula are connected to the perfusion system. The perfusion system begins with a constant monitoring of pressure, pH, oxygen partial pressure and electrolytic concentrations.

Following perfusion for a 24-hour period, the heart is removed and an autopsy is conducted. The autopsy results indicate that at least 90% of the tissue in the heart has maintained viability.

Example 2

The procedures used in Example 1 are followed with minor modifications. Circulation of perfusate through the surgically removed heart is performed in a closed loop wherein the solution is cooled and filtered. Fluid is then passed to a thermal regulator/debubbler via a membrane oxygenator where it is oxygenated with either 100% oxygen or 95% oxygen and 5% carbon dioxide. A portion of the perfusate in the thermal regulator unit is circulated through the pH sensor module to detect solution pH changes. From the thermal regulator/debubbler, the solution is pumped into the hydrostatic reservoir. The hydrostatic reservoir is designed to provide passive perfusate pressure to the heart in the event of pump failure. An overflow port on the reservoir prevents excess pressure buildup in the vessel and heart. The fluid passing through the port is directed into the base of the paracardial sac where the heart is suspended.

Pressurized flow from the hydrostatic chamber is directed through a 0-200 milliliter per minute rotameter, a 25 micrometer bubble trap and finally into the heart via a standard USCI arterial catheter. Perfusate exiting the right ventricle fills the top of the pericardial sac and is collected on the bottom of the heart chamber. A

recirculation loop is completed by pumping the fluid in the heart chamber back to the reservoir.

Maintenance of low perfusate temperatures, in the range of 5°C ± 1°C, is performed by two external refrigeration coolers connected to submersible Teflon®-coated copper coils in the perfusate reservoir and the thermal regulator/debubbler.

The perfusate pH is stabilized between 7.4 and 7.8 by intermittent gasification of the solution with a 95% oxygen/5% carbon dioxide mixture in the membrane oxygenator. A pH controller module detects pH variations by an electrode positioned in the pH sensor module. Values of pH above a threshold setting of 7.8 on the controller causes the module relay to activate a solenoid which then directs the membrane oxygenator inlet gas from 100% oxygen to 95% oxygen/5% carbon dioxide. The formation of carbonic acid in the perfusate, generated by carbon dioxide, acts to decrease the pH. Since the perfusate pH normally rises during these experiments, due to release of dissolved carbon dioxide, there is no need to increase the pH by addition of aqueous bases or the like.

This experiment was conducted using a perfusate solution containing an electrolyte concentration approximating extracellular or Krebs-Ringer solutions. The solution has been used by Copeland (C. J. Thorac. Cardiovascular Surgery, 92:238, 1986). The surgical procedure for removing the heart was similar to that outlined in Example 1.

The autopsy on the dog heart perfused and maintained in Example 2 revealed that ischemic changes were minimized and an index of viability was in the 97-99% range.

Example 3

In this example, a dog heart was surgically removed as described in Example 1 and perfused in accordance with the procedure outlined in Example 2. This example differs from the prior examples in that it represents the first implementation of normothermic perfusion using an FC-43 fluorocarbon emulsion in addition to hypothermic intracellular electrolyte perfusion. A 1-hour normothermic perfusion was performed immediately prior to and following the 24-hour hypothermic electrolyte perfusion.

The perfused canine heart exhibited excellent ventricular contractility at normothermic conditions after 24 hours. The extracellular and intracellular electrolyte solutions used are those found in Tables I and II, respectively. The autopsy results on the heart used in Example 3 were excellent, indicating very little damage or edema.

As is readily apparent from the above description of the total organ perfusion system of the present invention, the system may be used to maintain any number of donor organs, and is not restricted to use with human or animal hearts. It is also apparent that additional advantages and modifications of the present invention will readily occur to those skilled in the art. The invention in its broader aspects is therefore not limited to the specific details, representative apparatus, and the illustrative examples shown and described. Accordingly, departures may be made from the detail without departing from the spirit or scope of the disclosed general inventive concept.

WHAT IS CLAIMED IS:

1. A total organ perfusion system comprising

(a) a chamber for supporting an organ, said chamber being adapted to the continuous flow of one or more perfusion fluids;

(b) a primary perfusion system including a primary perfusion emulsion, said primary perfusion emulsion characterized by an oxygen transfer and transport capability that is functionally effective to maintain cellular viability of biological organs or tissue; and

(c) a secondary perfusion system for supplying one or more electrolyte fluids to said primary perfusion system.

2. The total organ perfusion system of claim 1 further comprising means for regulating the temperature of said primary perfusion emulsion.

3. The total organ perfusion system of claim 1 further comprising sensing means for measuring and controlling the oxygen concentration in said primary perfusion emulsion.

4. The total organ perfusion system of claim 1 further comprising sensing means for measuring and controlling the pH of said primary perfusion emulsion.

5. The total organ perfusion system of claim 1 further comprising sensing means for measuring and controlling the pressure of said primary perfusion emulsion.

6. The total organ perfusion system of claim 3 wherein said sensing means measures said oxygen concentration of said primary perfusion emulsion before said emulsion is introduced into an organ and after said emulsion exits from said organ.

7. The total organ perfusion system of claim 4 wherein said sensing means measures said pH of said primary perfusion emulsion before said emulsion is introduced into an organ and after said emulsion exits from said organ.

8. The total organ perfusion system of claim 5 wherein said sensing means measures said pressure of said primary perfusion emulsion before said emulsion is introduced into an organ and after said emulsion exits from said organ.

9. The total organ perfusion system of claim 1 further comprising oxygenating means for said primary perfusion emulsion.

10. The total organ perfusion system of claim 9 wherein said oxygenating means is a membrane oxygenator.

11. The total organ perfusion system of claim 1 further including an external filtering system which includes an

artificial kidney for filtering wastes from said primary perfusion emulsion.

12. The total organ perfusion system of claim 11 wherein said external filtering system includes at least one particulate filter for filtering wastes from said primary perfusion emulsion, prior to said emulsion being filtered through said artificial kidney.

13. The total organ perfusion system of claim 1 further comprising one or more reservoirs for storing said primary perfusion emulsion and one or more reservoirs for storing said one or more electrolyte fluids.

14. The total organ perfusion system of claim 13 further comprising a control loop enabling the fluids introduced into said organ chamber from one of said reservoirs to be transported to another reservoir prior to being filtered, after the volume of the fluid introduced into said organ chamber exceeds a predetermined amount.

15. The total organ perfusion system of claim 13 further comprising means enabling fluid exiting from one of said reservoirs to be filtered while fluid from another reservoir is introduced into said organ.

16. The total organ perfusion system of claim 1 wherein said primary perfusion emulsion includes one or more perfluorochemicals.

17. The total organ perfusion system of claim 1 further comprising means for adding nutrients to said primary perfusion emulsion.

18. The total organ perfusion system of claim 1, wherein said organ is a heart, further comprising means for artificially stimulating a heartbeat implanted in said heart.

19. The total organ perfusion system of claim 1, wherein said primary perfusion emulsion is a fluorocarbon pseudoplasma emulsion.

20. A method of maintaining an organ extracorporeally comprising:

(a) obtaining a donor organ;

(b) placing said organ in a chamber, said chamber being designed to support said organ;

(c) introducing a primary perfusion emulsion into said organ, said emulsion:

(i) providing nutrients to said organ;

(ii) providing oxygen to said organ in a form that enables transfer of said oxygen from said emulsion to said organ;

(iii) providing electrolyte fluids to said organ to maintain the predetermined ionic charge across the cell membranes comprising said organ; and

(d) filtering said primary perfusion emulsion to remove waste materials from said emulsion after said emulsion is expelled from said organ.

21. The method of claim 20 further compromising regulating the temperature of said primary perfusion emulsion.

22. The method of claim 20 further comprising measuring and controlling the oxygen concentration in said primary perfusion emulsion.

23. The method of claim 20 further comprising measuring and controlling the pH of said primary perfusion emulsion.

24. The method of claim 20 further comprising measuring and controlling the pressure of said primary perfusion emulsion.

25. The method of claim 22 wherein said measuring and controlling of said oxygen concentration of said primary perfusion emulsion occurs before said emulsion is introduced into said organ and after said emulsion exits from said organ.

26. The method of claim 23 wherein said measuring and controlling of said pH of said primary perfusion emulsion occurs before said emulsion is introduced into said organ and after said emulsion exits from said organ.

27. The method of claim 24 wherein said measuring and controlling of said pressure of said primary perfusion emulsion occurs before said emulsion is introduced into said organ and after said emulsion exits from said organ.

28. The method of claim 20 further comprising oxygenating said primary perfusion emulsion.

29. The method of claim 28 wherein said oxygenating occurs with a membrane oxygenator.

30. The method of claim 20 wherein said filtering occurs in an artificial kidney for filtering wastes from said primary perfusion emulsion.

31. The method of claim 30 wherein said filtering also occurs in at least one particulate filter for filtering wastes from said primary perfusion emulsion, prior to said emulsion being filtered through said artificial kidney.

32. The method of claim 20 further comprising storing said primary perfusion emulsion in one or more reservoirs and storing one or more electrolyte fluids in separate storage tanks.

33. The method of claim 32 further comprising using a control loop to enable the fluid introduced into said organ chamber from one of said reservoirs to be transported to another reservoir prior to being filtered, after the volume of the fluid introduced into said organ chamber exceeds a predetermined amount.

34. The method of claim 32 further comprising filtering fluid exiting from one of said reservoirs while feeding fluid from another reservoir to said organ.

35. The method of claim 20 wherein said primary perfusion emulsion includes a perfluorochemical.

36. The method of claim 20 further comprising adding nutrients to said primary perfusion emulsion.

37. The method of claim 20, wherein said organ is a heart, further comprising maintaining an artificially stimulated heartbeat.

38. The method of claim 20, wherein said primary perfusion emulsion is a fluorocarbon primary perfusion emulsion.

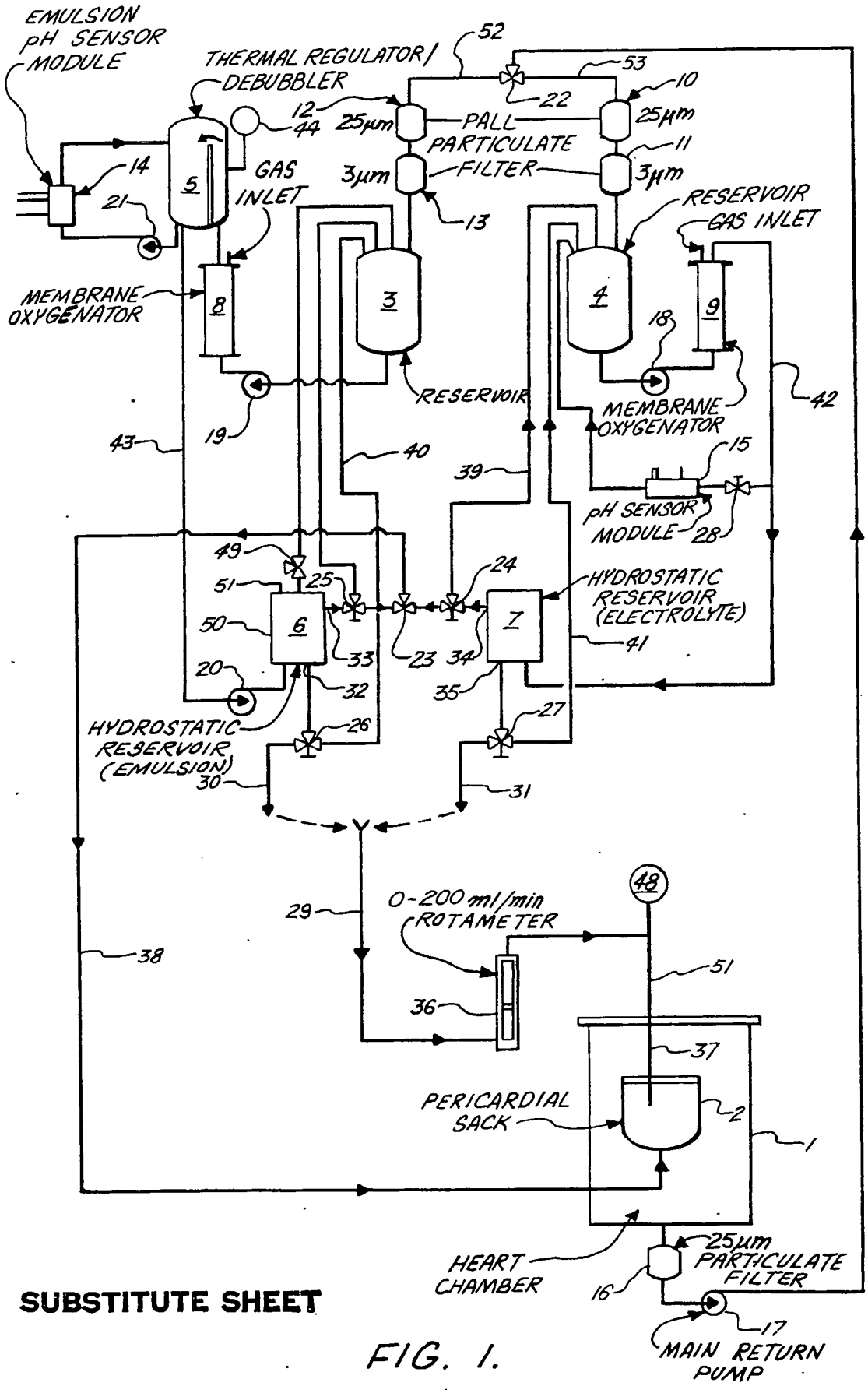
EMULSION pH SENSOR MODULE
THERMAL REGULATOR/ DEBUBBLER
52
53
10
22
12
44
25μm
PALL PARTICULATE FILTER
25μm
11
3μm
3μm
14
5
GAS INLET
21
13
RESERVOIR GAS INLET
MEMBRANE OXYGENATOR
8
3
4
9
18
RESERVOIR
MEMBRANE OXYGENATOR
42
43
19
40
39
15
pH SENSOR MODULE
28
49
24
51
25
HYDROSTATIC RESERVOIR (ELECTROLYTE)
50
6
7
41
33
23
34
20
32
35
27
HYDROSTATIC RESERVOIR (EMULSION)
26
30
31
48
29
0-200 ml/min ROTAMETER
38
51
36
37
PERICARDIAL SACK
2
1
HEART CHAMBER
25μm PARTICULATE FILTER
16
17
MAIN RETURN PUMP

FIG. 1.

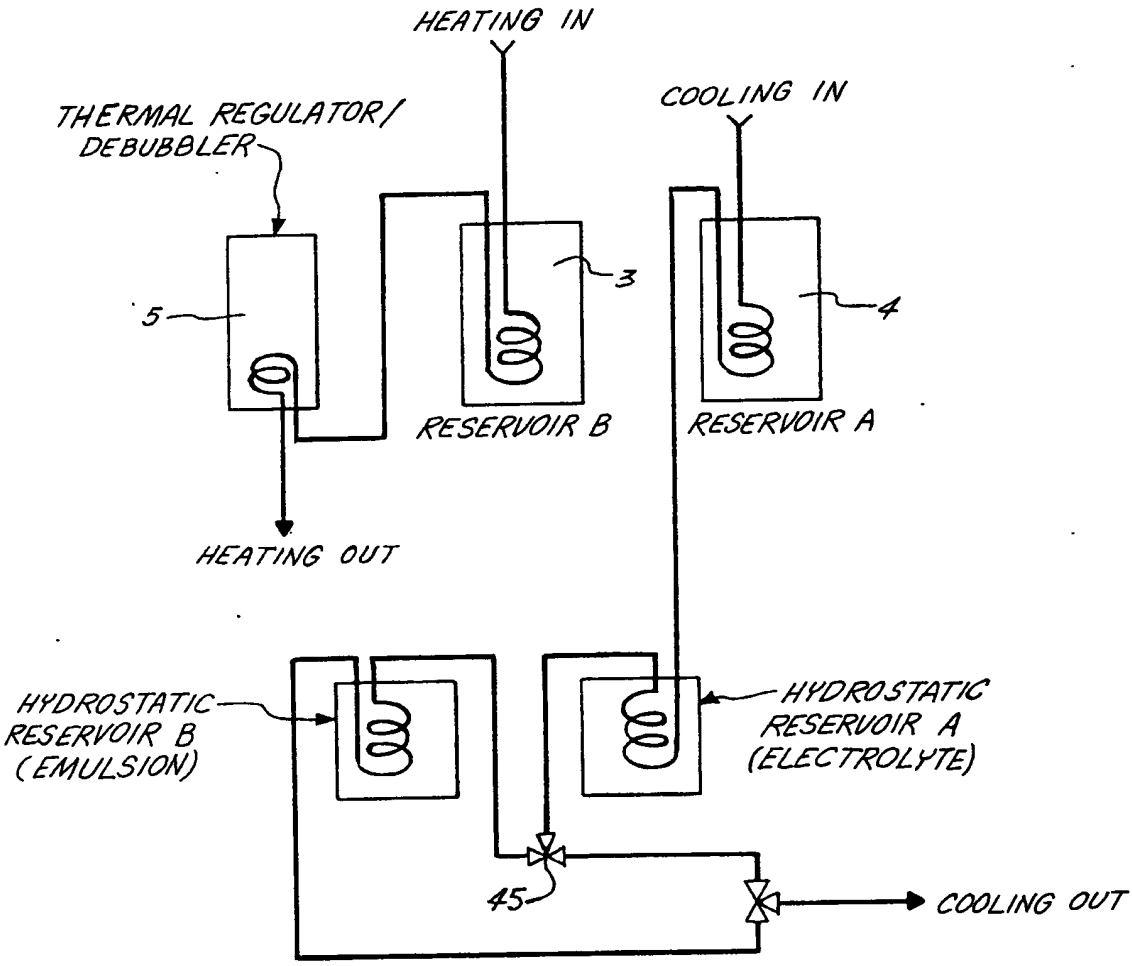
HEATING IN
COOLING IN
THERMAL REGULATOR/
DEBUBBLER
5
3
4
RESERVOIR B
RESERVOIR A
HEATING OUT
HYDROSTATIC
RESERVOIR B
(EMULSION)
HYDROSTATIC
RESERVOIR A
(ELECTROLYTE)
45
COOLING OUT

FIG. 2.

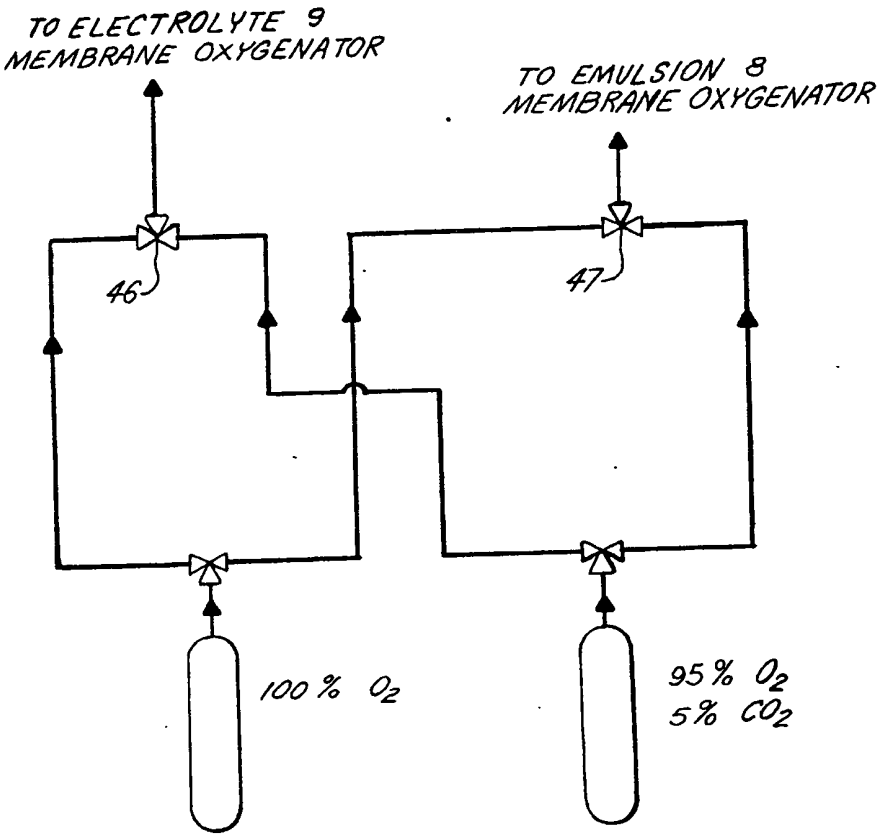
TO ELECTROLYTE 9
MEMBRANE OXYGENATOR
TO EMULSION 8
MEMBRANE OXYGENATOR
46
47
100 % O_2
95 % O_2
5 % CO_2

FIG. 3.

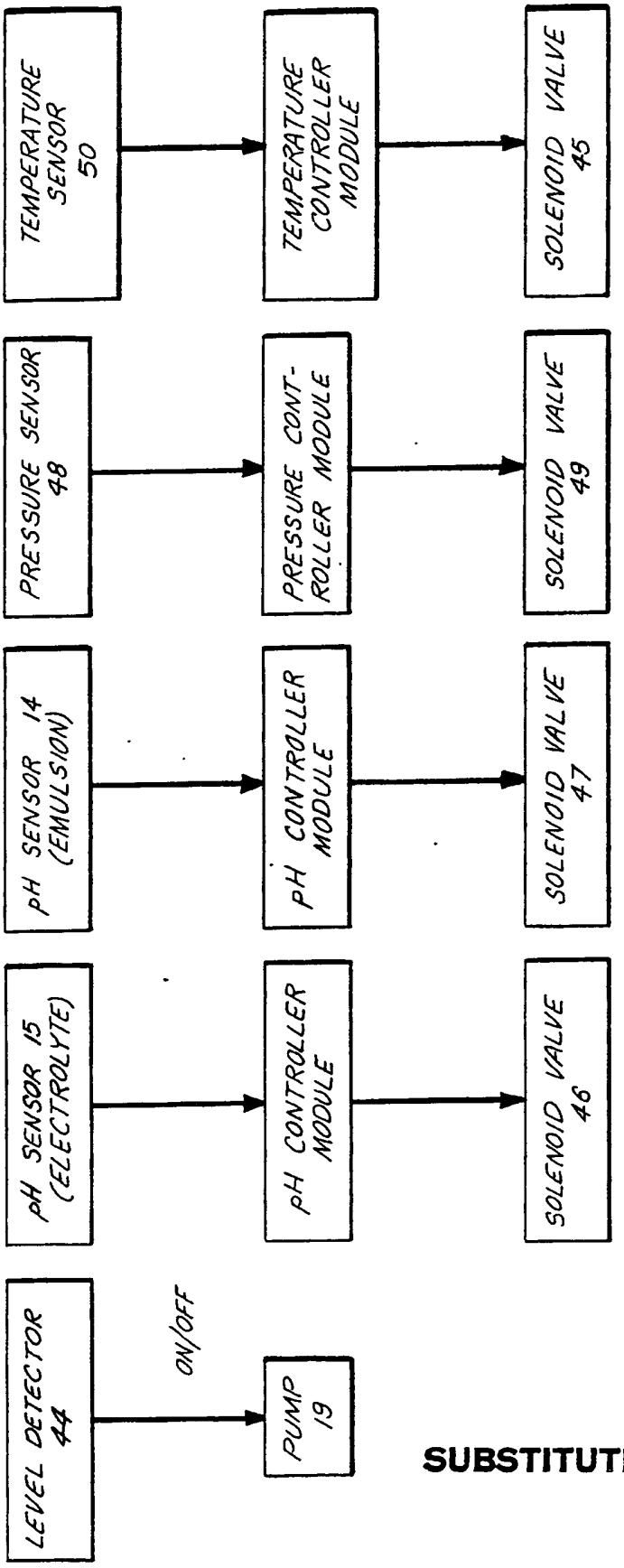
TEMPERATURE SENSOR 50
TEMPERATURE CONTROLLER MODULE
SOLENOID VALVE 45
PRESSURE SENSOR 48
PRESSURE CONT-ROLLER MODULE
SOLENOID VALVE 49
pH SENSOR 14 (EMULSION)
pH CONTROLLER MODULE
SOLENOID VALVE 47
pH SENSOR 15 (ELECTROLYTE)
pH CONTROLLER MODULE
SOLENOID VALVE 46
LEVEL DETECTOR 44
ON/OFF
PUMP 19

FIG. 4.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/00103

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (4): A01N 1/02
U.S. Cl. 435/1,283

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System [5]	Classification Symbols
U.S.	435/1, 2, 3, 283, 289, 290, 291, 311, 313; 128/204.17, 204.18, 204.22; 604/4, 5

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category * [15]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	"Potential Uses of Perfluorochemical Artificial Blood for Experimental Studies in Physiology, Biology, Biochemistry, Chemotherapy, Toxicology, Metabolism, etc.: FC-43 Emulsion", published 1976, September 4, by The Green Cross Corporation (Osaka, Japan), Technical Information Ser. No. 3, see pages 1 to 20 especially pages 1 to 3, 11 to 13, 17 and 18.	1-38
Y,P	US, A, 4,713,055 (VIGGIANO) 15 December 1987 (15.12.87), see column 1, line 23 to column 2, line 65 and column 3, line 28 to column 4, line 9.	1-38
Y	US, A, 4,105,798 (MOORE ET AL.) 08 August 1978 (08.08.78), see column 1, line 23 to column 2, line 14, column 3, line 63 to column 4, line 5 and claims 1 and 26.	1-38
Y	US, A, 3,911,138 (CLARK, JR.) 07 October 1975 (07.10.75), see column 1, lines 22 to 30, column 2, lines 27 to 46 and claim 19.	1-38

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [9]
07 April 1988	02 MAY 1988
International Searching Authority [1]	Signature of Authorized Officer [10]
ISA/US	Randall E. Deck

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US, A, 3,772,153 (DE ROISSART) 13 November 1973 (13.11.73), see column 3, line 51 to column 5, line 8.	1-38
A	US, A, 3,753,865 (BELZER ET AL.) 21 August 1973 (21.08.73), see Figure 11.	1-38
A	EP, A2, 125,847 (RENEAU) 21 November 1984 (21.11.84), see pages 3 to 7.	1-38

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers_____, because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers_____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.